

# Partial Resuscitative Endovascular Balloon Occlusion of the Aorta in Swine Model of Hemorrhagic Shock



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- BACKGROUND:** Complete resuscitative endovascular balloon occlusion of the aorta (C-REBOA) increases proximal mean arterial pressure (MAP) at the cost of distal organ ischemia, limiting the duration of intervention. We hypothesized that partial aortic occlusion (P-REBOA) would maintain a more physiologic proximal MAP and reduce distal tissue ischemia. We investigated the hemodynamic and physiologic effects of P-REBOA vs C-REBOA.
- STUDY DESIGN:** Fifteen swine were anesthetized, instrumented, splenectomized, and subjected to rapid 25% blood volume loss. They were randomized to C-REBOA, P-REBOA, or no intervention (controls). Partial REBOA was created by partially inflating an aortic balloon catheter to generate a 50% blood pressure gradient across the balloon. Hemodynamics were recorded and serum markers of ischemia and inflammation were measured. After 90 minutes of treatment, balloons were deflated to evaluate the immediate effects of reperfusion. End organs were histologically examined.
- RESULTS:** Complete REBOA produced supraphysiologic increases in proximal MAP after hemorrhage compared with more modest augmentation in the P-REBOA group ( $p < 0.01$ ), with both groups significantly greater than controls ( $p < 0.01$ ). Less rebound hypotension after balloon deflation was seen in the P-REBOA compared with C-REBOA groups. Complete REBOA resulted in higher serum lactate than both P-REBOA and controls ( $p < 0.01$ ). Histology revealed early necrosis and disruption of duodenal mucosa in all C-REBOA animals, but none in P-REBOA animals.
- CONCLUSIONS:** In a porcine hemorrhagic shock model, P-REBOA resulted in more physiologically tolerable hemodynamic and ischemic changes compared with C-REBOA. Additional work is needed to determine whether the benefits associated with P-REBOA can both extend the duration of intervention and increase survival. (*J Am Coll Surg* 2016;223:359–368. Published by Elsevier Inc. on behalf of the American College of Surgeons. This is an open access article under the CC BY-NC-ND license [<http://creativecommons.org/licenses/by-nc-nd/4.0/>].)

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**Abbreviations and Acronyms**

C-REBOA	= complete resuscitative endovascular balloon occlusion of the aorta
IL	= interleukin
MAP	= mean arterial pressure
P-REBOA	= partial resuscitative endovascular balloon occlusion of the aorta
REBOA	= resuscitative endovascular balloon occlusion of the aorta

Hemorrhage is one of the leading causes of death in civilian and military trauma,<sup>1-3</sup> and mortality increases 7% for every 15 minutes that passes without definitive hemorrhage control.<sup>4</sup> However, transport times to reach trauma facilities frequently exceed 1 hour, and combat scenarios can require prolonged periods of prehospital field care.<sup>5</sup>

Resuscitative endovascular balloon occlusion of the aorta (REBOA) has emerged as a less invasive alternative to resuscitative thoracotomy with aortic cross-clamping for the treatment of patients in extremis from noncompressible hemorrhage. The less invasive nature of this catheter-based approach, coupled with the ability to proactively use this intervention before hemodynamic collapse, has resulted in a survival benefit over open aortic cross-clamping in early translational research and clinical experience.<sup>6,7</sup> Although in the United States REBOA is used primarily in fully resourced Level I trauma centers, this technique has the potential to be adapted for use in more-austere environments and for longer periods of time.<sup>8</sup>

Yet, the advantage of earlier intervention with REBOA is limited by the consequences of prolonged aortic occlusion.<sup>9-12</sup> Although REBOA can confer a short-term survival advantage by preventing exsanguination and augmenting perfusion of the heart, lungs, and brain, it is also associated with substantial morbidity from ischemia distal to the balloon.<sup>7,13</sup> Periods of occlusion exceeding 40 minutes can result in irreversible organ injury and death.<sup>9-11</sup> Additionally, supraphysiologic increases in blood pressure proximal to the occlusion balloon during complete REBOA (C-REBOA) can contribute to cardiac failure and exacerbation of traumatic brain injury.<sup>14-17</sup>

The morbidity associated with C-REBOA has led to the search for alternate endovascular approaches that still achieve effective hemorrhage control and mitigate the adverse effects of proximal hypertension and distal ischemia.<sup>18</sup> Intermittent balloon deflation regimens to perfuse distal tissue beds and limit ischemia have offered

little benefit over C-REBOA in animal models and in clinical practice.<sup>9,12</sup> An alternative to this binary approach to aortic blood flow (ie complete occlusion alternating with no occlusion) is continuous, low-volume, distal perfusion achieved through partial aortic occlusion. This approach, termed *partial REBOA* (P-REBOA), is based on a previously described neurointerventional radiology technique of using partially occlusive balloon catheters to augment cerebral perfusion in stroke patients, and has only recently been attempted in the presence of noncompressible torso hemorrhage.<sup>19-24</sup> The physiologic impact of P-REBOA for sustained therapy in hemorrhagic shock has not been fully characterized. In an effort to test this effect, we hypothesized P-REBOA would preserve proximal aortic mean arterial pressure (MAP) closer to normal physiologic levels and concurrently reduce distal ischemia and systemic metabolic injury compared with C-REBOA in a porcine hemorrhagic shock model.

**METHODS****Overview**

This study was approved by the Institutional Animal Care and Use Committee at David Grant USAF Medical Center, Travis Air Force Base, Fairfield, CA. All animal care and use was in strict compliance with the *Guide for the Care and Use of Laboratory Animals* in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. Healthy adult, castrate male and nonpregnant female Yorkshire-cross swine (*Sus scrofa*) obtained from the University of California, Davis, were acclimated for a minimum of 7 days. At the time of experimentation, animals were between 5 and 7 months of age, with a mean weight of 102 kg ( $\pm 5$  kg).

**Animal preparation**

Animals were premedicated with 6.6 mg/kg tiletamine/zolazepam (Telazol; Fort Dodge Animal Health) intramuscularly. After isoflurane induction and endotracheal intubation, maintenance anesthesia consisted of 2% isoflurane in 100% oxygen. Animals were mechanically ventilated with tidal volumes of 7 to 10 mL/kg and a respiratory rate of 10 to 15 breaths per minute sufficient to maintain end tidal CO<sub>2</sub> at  $40 \pm 5$  mmHg. The pigs were placed on a warming blanket set at 39°C to maintain body temperature.

Both carotid arteries were exposed through a midline neck incision, and the femoral arteries were accessed through separate oblique groin incisions. Arterial access was obtained for controlled hemorrhage, hemodynamic monitoring, and to facilitate endovascular intervention.

Proximal aortic MAP was measured via a 6F 30-cm introducer sheath (Super Sheath, Boston Scientific Corporation) inserted in the left common carotid artery, with the tip positioned under fluoroscopic guidance at the level of the proximal descending thoracic aorta. Distal aortic pressure was similarly obtained via a 6F 30-cm introducer sheath (Super Sheath) inserted retrograde via the right femoral artery, with the tip residing within the infrarenal abdominal aorta. A 6F 13-cm sheath was inserted retrograde into the right common carotid artery (Super Sheath) to enable controlled hemorrhage. Additionally, a 12F 13-cm introducer sheath (Cook Incorporated) was inserted retrograde into the left femoral artery, through which the occlusion balloon catheter was introduced.

Concurrently, a laparotomy was performed. A splenectomy was completed to minimize hemodynamic variation from autotransfusion, and a Foley catheter was inserted into the bladder via cystotomy. A 5F 10-cm micropuncture sheath (Cook Incorporated) was inserted retrograde into a distal jejunal branch of the superior mesenteric artery for visceral arterial pressure monitoring. Procedural blood loss was quantified and the abdomen was closed before initiation of hemorrhage. An aortogram was performed to measure the aortic diameter at the level of the diaphragm using a radiopaque sizing catheter (AccuVue; Angiodynamics).

### Hemorrhage

During a 20-minute period, 25% of the estimated total blood volume ( $66 \text{ mL/kg} \times 0.25 = 16.5 \text{ mL/kg}$ ) was evacuated from the right carotid intravascular sheath. To overcome the vasodilatory effects of general anesthesia, an intravenous infusion of norepinephrine ( $0.01 \mu\text{g/kg/h}$ ) was initiated. Normal saline was then administered at  $10 \text{ mL/kg/h}$ . At the conclusion of hemorrhage, a repeat aortogram was performed to measure the change in aortic diameter induced by hypovolemic shock.

### Intervention

Animals were then assigned to control, C-REBOA, or P-REBOA via a block randomization scheme. Resuscitative endovascular balloon occlusion of the aorta was performed using a noncompliant 80-mm balloon catheter (Armada; Abbott Laboratories Vascular Enterprises). The balloon was advanced over a stiff guide wire into the descending thoracic aorta, and its position at the level of the diaphragm was confirmed by fluoroscopy. The balloon catheter was secured in position, but was not inflated in the control group. In the C-REBOA group, a balloon with a nominal diameter 2 mm greater than that of the shock-state aorta was inflated until pulsatile

distal aortic pressure was lost. In the P-REBOA group, a balloon with a nominal diameter equal to that of the shock-state aorta was partially inflated until a 50% proximal to distal aortic pressure gradient was achieved. This aortic pressure gradient was measured and maintained continuously throughout the experiment by manual adjustment of balloon inflation volume. Balloon inflation was performed with a standard balloon inflation device (Encore Advantage Kit; Boston Scientific Corporation). The moment of balloon inflation was designated as time zero. Balloons remained inflated for 90 minutes in the intervention groups and uninflated in the control group. After the 90-minute intervention period, balloons in the intervention groups were incrementally deflated for 2 minutes. After balloon deflation, animals were monitored for an additional 15 minutes before being euthanized to examine the immediate effects of reperfusion. Physiologic data were continuously captured throughout the experiment using a multichannel recorder (MP150; Biopac Systems Incorporated). Analyzed data included proximal and distal aortic pressures, visceral arterial pressure, core body temperature, and ECG monitoring.

Arterial blood gas measurements were performed at baseline (immediately pre hemorrhage), every 15 minutes for 90 minutes, and then every 5 minutes to the end of the study. Complete blood counts, basic metabolic assays, and serum cytokine analysis (tumor necrosis factor- $\alpha$ , interleukin [IL] 6, IL8, IL10, and heat shock protein 90; Quantikine ELISA; R&D Systems) were performed at baseline and then every 30 minutes for 90 minutes. All animals underwent necropsy with samples from hind-limb adductor muscles, duodenum, renal parenchyma, myocardium, and brain preserved in 10% buffered formalin solution, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for histopathologic evaluation by a pathologist blinded to the intervention.

### Data analysis

Data are presented as mean  $\pm$  SEM, unless otherwise specified, and were analyzed using repeated measures ANOVA with post-hoc pairwise comparisons, when indicated, using standard statistical software (STATA, version 13.0, Stata Corp). Statistical significance was set at  $p < 0.05$ .

### RESULTS

Baseline characteristics of animals in the C-REBOA, P-REBOA, and control groups are shown in [Table 1](#). There were no significant differences in baseline anatomic, hemodynamic, and physiologic values among

**Table 1.** Baseline Physiologic and Hematologic Parameters by Treatment Group

Value	Resuscitative endovascular balloon occlusion of the aorta		Control	p Value
	Complete	Partial		
n	5	5	5	
Weight, kg, mean $\pm$ SEM	92 $\pm$ 7.6	100 $\pm$ 10.7	115 $\pm$ 6.9	0.20
Sex, male:female, n	3:2	3:2	2:3	0.77
Physiologic parameter, mean $\pm$ SEM				
Temperature, $^{\circ}$ C	35.9 $\pm$ 0.2	36.2 $\pm$ 0.3	36.4 $\pm$ 0.2	0.34
Preoperative blood loss, mL/kg	2.0 $\pm$ 0.5	1.2 $\pm$ 0.3	1.9 $\pm$ 0.5	0.38
Heart rate, beats/min	84 $\pm$ 4	72 $\pm$ 4	72 $\pm$ 3	0.07
Systolic blood pressure, mmHg	84 $\pm$ 4	80 $\pm$ 5	76 $\pm$ 11	0.74
Proximal aortic MAP, mmHg	74 $\pm$ 3	65 $\pm$ 5	65 $\pm$ 8	0.48
Distal aortic MAP, mmHg	72 $\pm$ 3	66 $\pm$ 4	68 $\pm$ 8	0.66
Visceral MAP, mmHg	71 $\pm$ 4	65 $\pm$ 5	66 $\pm$ 7	0.64
Spleen weight, g	927 $\pm$ 124	877 $\pm$ 86	857 $\pm$ 202	0.96
Hematologic parameter, mean $\pm$ SEM				
WBC, $\times 10^9$ /L	13.6 $\pm$ 1.5	16.8 $\pm$ 1.5	15.0 $\pm$ 1.9	0.41
Hemoglobin, g/dL	10.2 $\pm$ 0.6	11.4 $\pm$ 0.6	11.3 $\pm$ 0.5	0.31
Platelets, $\times 10^9$ /L	238 $\pm$ 28	246 $\pm$ 24	231 $\pm$ 27	0.92
Lactate, mmol/L	1.9 $\pm$ 0.2	1.7 $\pm$ 0.2	2.2 $\pm$ 0.3	0.32
pH	7.47 $\pm$ 0.0	7.52 $\pm$ 0.0	7.47 $\pm$ 0.0	0.10
Total protein, g/dL	5.5 $\pm$ 0.1	5.7 $\pm$ 0.1	5.6 $\pm$ 0.1	0.28

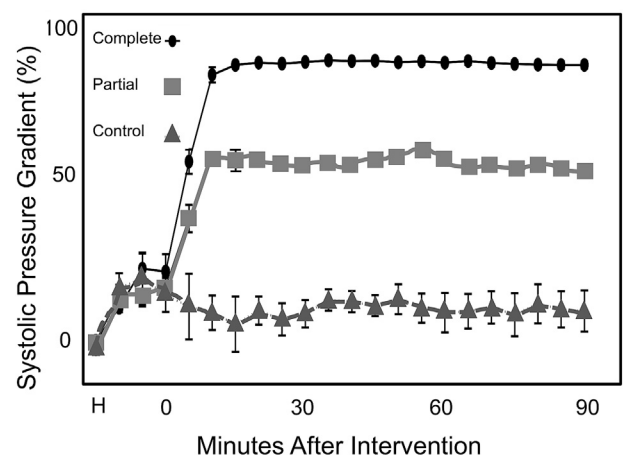
MAP, mean arterial pressure.

the groups. Consistent pressure gradients were maintained between proximal and distal systolic pressures in each treatment group, averaging 90% in the C-REBOA, 50% in the P-REBOA, and 10% in control groups (Fig. 1).

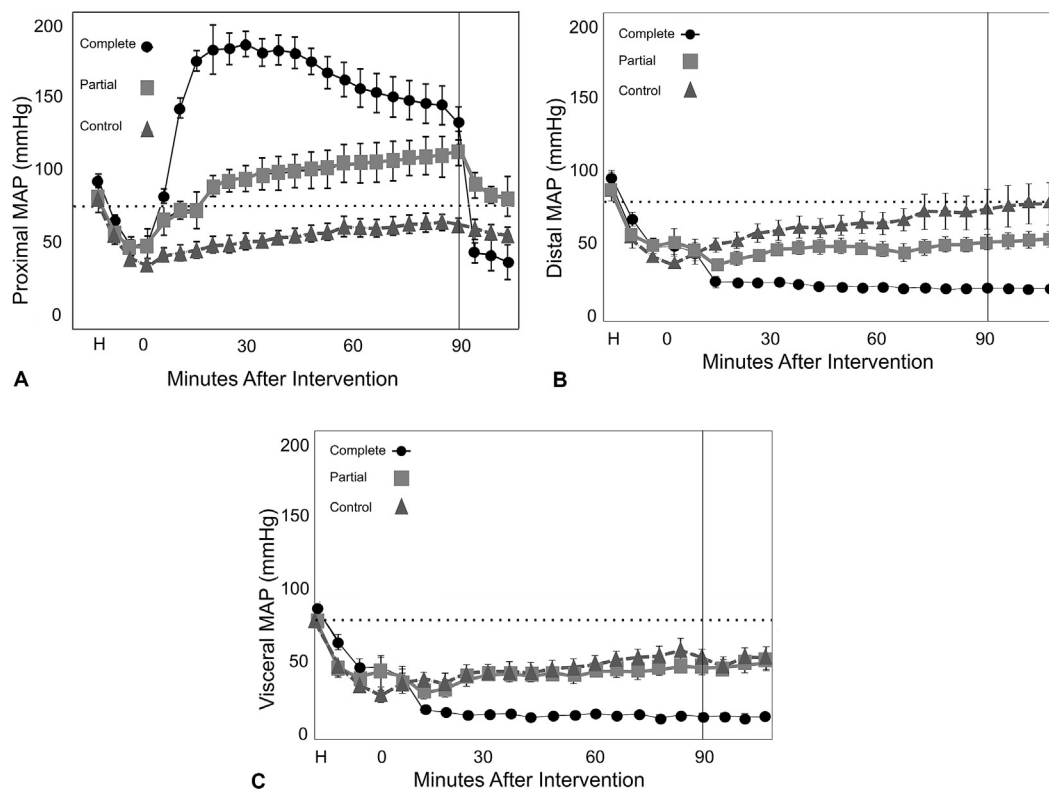
At 60 minutes, P-REBOA resulted in a proximal aortic MAP closer to baseline than either the C-REBOA or control group (+13.5 vs +69.0 and  $-20.2$  mmHg, respectively;  $p < 0.01$ ) (Fig. 2A). Distal MAP during intervention in the P-REBOA group was equivalent to controls ( $p = 0.47$ ), and distal MAP in the C-REBOA group was significantly decreased compared with either the P-REBOA or control groups ( $p < 0.01$ ) (Fig. 2B). Similarly, visceral MAP during intervention in the P-REBOA group was equivalent to controls ( $p = 0.62$ ), and visceral MAP in the C-REBOA group was significantly lower than either the P-REBOA or control groups ( $p = 0.01$ ) (Fig. 2C). On balloon deflation, aortic pressure gradients rapidly dissipated in both the C-REBOA and P-REBOA groups.

Serum lactate levels increased significantly ( $p < 0.05$ ) during the course of the study period in each group relative to baseline, and levels in the P-REBOA group remained equivalent to control throughout the intervention phase ( $p = 0.96$ ) (Fig. 3). Lactate concentration in the C-REBOA group rose continuously, nearly triple

the lactate concentration observed in either the P-REBOA or control groups by 90 minutes (9.3 vs 3.2 and 3.2, respectively;  $p < 0.01$ ). During the first 5 minutes of reperfusion in both the C-REBOA and P-REBOA



**Figure 1.** Comparison of differential proximal (cranial to balloon) and distal (caudal to balloon) aortic systolic blood pressure differential among complete resuscitative endovascular balloon occlusion of the aorta, partial resuscitative endovascular balloon occlusion of the aorta, and control groups. Differential pressures were significantly different among the groups ( $p < 0.01$ ). H, onset of hemorrhage.



**Figure 2.** (A) Comparison among mean arterial pressure (MAP) in the proximal (cranial to balloon) aorta in complete resuscitative endovascular balloon occlusion of the aorta (C-REBOA), partial resuscitative endovascular balloon occlusion of the aorta (P-REBOA), and control groups. Mean arterial pressures were significantly different among the groups ( $p < 0.01$ ). (B) Comparison of MAP in the distal (caudal to balloon) aorta among C-REBOA, P-REBOA, and control groups. Mean arterial pressures were significantly different between P-REBOA and control ( $p = 0.03$ ), and both were significantly different from C-REBOA ( $p < 0.01$ ). (C) Comparison of MAP in a standardized jejunal branch of the superior mesenteric artery (caudal to balloon) among C-REBOA, P-REBOA, and control groups. Mean arterial pressures were equivalent between P-REBOA and control ( $p = 0.12$ ), and both were significantly different from C-REBOA ( $p < 0.01$ ). H, onset of hemorrhage. Dashed line, baseline MAP. Vertical line, balloon deflation.

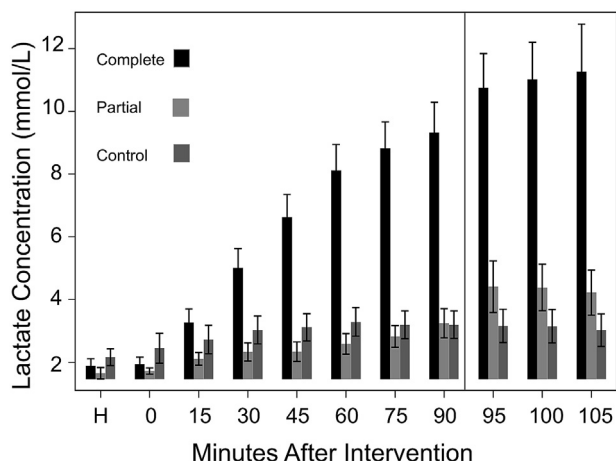
arms, serum lactate concentration increased above the highest levels reached during the intervention phase (Fig. 3). As washout of distal tissue beds continued, lactate levels quickly stabilized in the P-REBOA group, but continued to rise in the C-REBOA group. Serum lactate concentration peaked at 13.3 mmol/L in the C-REBOA group during reperfusion, which was more than double the concentrations seen in the P-REBOA group or control group by the end of the study ( $p < 0.01$ ).

Additional findings among the groups at 90 minutes include a more severe acidosis and a profound leukopenia in the C-REBOA group compared with the P-REBOA group or control group ( $p < 0.01$ ). Within each group, WBC, hemoglobin concentration, platelet count, pH, and total protein concentration decreased significantly (Table 2). Production of inflammatory cytokines

increased in all 3 groups from baseline to the end of intervention, but none reached statistical significance except for IL6 and IL10 in the C-REBOA group ( $p < 0.01$  and  $p = 0.02$ , respectively). There were no significant differences in cytokine concentration across the groups at any time point.

Histologic examination of the duodenum showed ischemic necrosis of the villous tips in 100% (5 of 5) of the C-REBOA group, 60% (3 of 5) of the control group, and only 20% (1 of 5) of the P-REBOA group ( $p = 0.04$ ), which included mucosal loss, lamina propria congestion, leukocyte infiltration, and loss of staining, with sparing of the deeper crypts (Fig. 4). Examination of renal parenchyma revealed foci of acute tubular necrosis in 80% (4 of 5) of the animals in the C-REBOA group and no significant ischemic changes noted in either the P-REBOA group or control group.





**Figure 3.** Blood lactate concentrations at various time points among complete resuscitative endovascular balloon occlusion of the aorta (C-REBOA), partial resuscitative endovascular balloon occlusion of the aorta (P-REBOA), and control groups. Blood lactate concentrations were significantly higher in the C-REBOA than P-REBOA and control groups ( $p < 0.01$ ), but were statistically equivalent in the P-REBOA and control groups ( $p = 0.66$ ). H, lactate concentration at the onset of hemorrhage.

All but one animal survived the duration of the experiment. The only death occurred in the C-REBOA group immediately after balloon deflation at 90 minutes.

## DISCUSSION

Resuscitative endovascular balloon occlusion of the aorta is emerging as a viable alternative to open aortic cross-clamping for hemorrhagic shock. This technique has been embraced by several Level I trauma centers throughout the United States and is being used internationally. Although REBOA is effective at limiting exsanguination and restoring proximal perfusion pressure to the heart, brain, and lungs, it results in a cumulative physiologic insult over time that can have detrimental consequences.<sup>10</sup> The supraphysiologic proximal pressures and afterload seen with REBOA can result in cardiac dysfunction or exacerbation of traumatic brain injury.<sup>14,16</sup> Additionally, intervention times in excess of 40 to 60 minutes can result in irreversible ischemia to distal tissues, with profound ischemia-reperfusion injury.<sup>9-11</sup> Partial REBOA can mitigate the adverse effects of sustained complete aortic occlusion and increase the maximal duration of intervention through the early restoration of distal blood flow.

In this study, we have demonstrated that P-REBOA maintained proximal MAP at more physiologically normal levels during intervention and after balloon deflation, and avoided the hemodynamic extremes seen with

C-REBOA. Partial REBOA also simultaneously maintained enough distal perfusion to minimize organ ischemia and the systemic burden of ischemia-reperfusion injury compared with C-REBOA.

Maintaining proximal MAP within a normal physiologic range with P-REBOA can reduce the incidence of cardiac dysfunction, cerebral edema, and respiratory failure compared with sustained aortic occlusion.<sup>9,10</sup> Beginning at balloon inflation, C-REBOA produces supraphysiologic augmentation of proximal aortic MAP with dramatic increases in cardiac afterload, even in the context of hypovolemic shock. Proximal MAP as high as 222 mmHg was seen in the C-REBOA arm of our study. Supraphysiologic MAP  $>110$  mmHg persisted in all animals in the C-REBOA arm as long as the balloon remained inflated. This dramatic increase in aortic afterload might be detrimental to cardiac performance, particularly in the context of an already ischemic or injured myocardium.<sup>15,16,25</sup> The downtrend in proximal MAP seen in the C-REBOA arm might represent declining cardiac function during the course of the experiment. This trend was not seen in the P-REBOA or control arms. Additionally, these supraphysiologic proximal pressures can exacerbate concomitant blunt aortic, brain, or pulmonary injuries.<sup>17,25-28</sup> Therapies aimed at preserving hemodynamics within a normal physiologic range can result in less end-organ damage and increase the potential number of patients that can benefit from these treatments.

Partial REBOA can also offer a way to extend the duration of intervention beyond what is currently possible with C-REBOA. Partial REBOA reduced the systemic metabolic burden of ischemia and inflammation compared with the C-REBOA group. Buildup of lactic acid and resultant metabolic acidosis were less severe in the P-REBOA group than the C-REBOA group, both from the lessened tissue ischemia and a continuous washout of metabolites provided by preserved distal perfusion. Additionally, white cell sequestration in ischemic distal tissue beds created a profound leukopenia in the C-REBOA group that worsened as the study progressed and was not seen in either the P-REBOA group or control group. Although this sequestration phenomenon is not fully understood, leukopenia in trauma patients has been associated with worse outcomes.<sup>29-31</sup> In addition, P-REBOA preserved distal blood flow sufficient to avoid the significant duodenal and kidney ischemia seen in the C-REBOA group.

Unexpectedly, there was less duodenal ischemia in the P-REBOA group than in the control group, despite equivalent visceral MAP. This finding suggests that P-REBOA can induce resistance to ischemic organ injury at the cellular level, similar to remote ischemic

**Table 2.** Physiologic and Hematologic Parameters by Treatment Group after 90 Minutes of Treatment

	Resuscitative endovascular balloon occlusion of the aorta, mean ± SEM			
Value	Complete	Partial	Control, mean ± SEM	p Value
Physiologic parameter				
Temperature, °C	34.8 ± 0.2	35.2 ± 0.1	35.3 ± 0.4	0.39
Total blood loss, mL/kg	16.7 ± 0.2	16.5 ± 0.0	16.4 ± 0.1	0.26
Total crystalloid, mL	3,311 ± 669	2,543 ± 594	2,225 ± 571	0.49
Norepinephrine infusion, mL	0.9 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	0.24
Hematologic parameter				
WBC, × 10 <sup>9</sup> /L	7.9 ± 0.7 <sup>*,†,‡</sup>	15.2 ± 1.8	14.4 ± 1.4	<0.01
Hemoglobin, g/dL	8.4 ± 0.4 <sup>‡</sup>	8.6 ± 0.5 <sup>‡</sup>	8.6 ± 0.5 <sup>‡</sup>	0.93
Platelets, × 10 <sup>9</sup> /L	180 ± 10	201 ± 24	197 ± 21	0.72
Lactate, mmol/L	9.3 ± 1.0 <sup>*,†,‡</sup>	3.2 ± 0.5	3.2 ± 0.4	<0.01
pH	7.33 ± 0.04 <sup>*,†,‡</sup>	7.42 ± 0.01 <sup>‡</sup>	7.44 ± 0.02	0.02
Total protein, g/dL	4.5 ± 0.1 <sup>*,‡</sup>	4.3 ± 0.1 <sup>‡</sup>	4.1 ± 0.1 <sup>‡</sup>	0.02

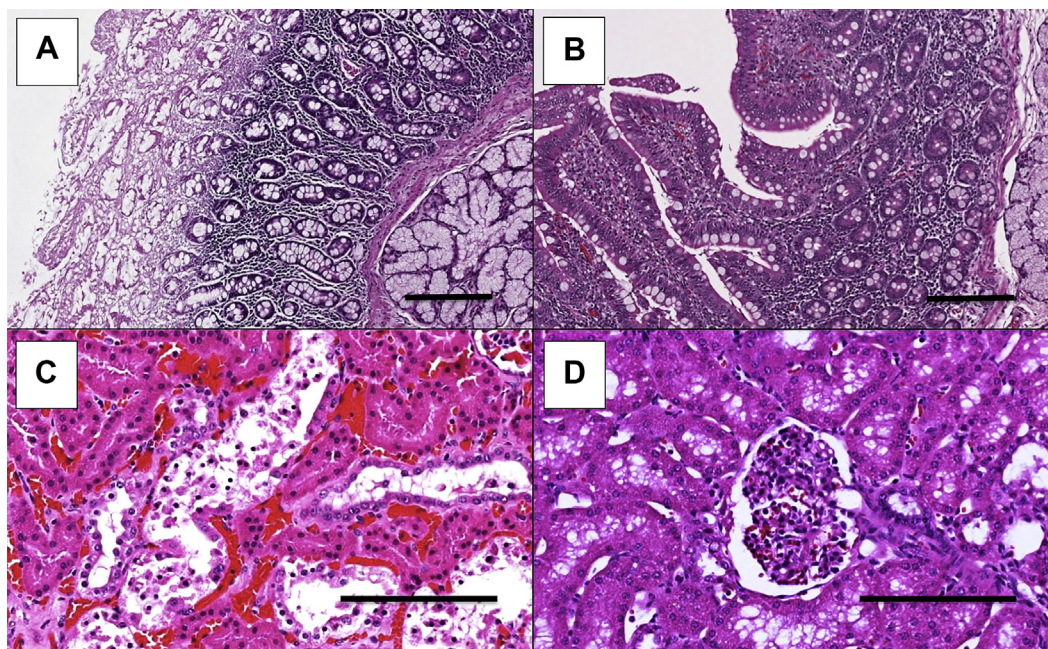
\*Significantly different from control,  $p < 0.05$ .

<sup>†</sup>Significantly different from partial,  $p \leq 0.05$ .

<sup>‡</sup>Significantly different from baseline,  $p < 0.05$ .

preconditioning. Remote ischemic preconditioning, although not fully understood, is the intentional creation of transient, tolerable limb ischemia before coronary intervention. This technique is hypothesized to have a

cardioprotective effect that can reduce the risk of subsequent infarction, stroke, and all-cause mortality.<sup>32,33</sup> Studies suggest that the cardioprotection provided by remote ischemic preconditioning might be only one



**Figure 4.** (A) Photomicrograph of duodenal microvilli from a representative C-REBOA animal showing coagulation necrosis of approximately 50% of the mucosal cells, 100 $\times$ ; scale bar = 50  $\mu$ m. (B) Photomicrograph of duodenal microvilli from a representative P-REBOA animal showing normal mucosa, 100 $\times$ ; scale bar = 50  $\mu$ m. (C) Photomicrograph of renal cortex from a representative C-REBOA animal showing acute tubular necrosis, 400 $\times$ ; scale bar = 50  $\mu$ m. (D) Photomicrograph of renal cortex from a representative P-REBOA showing normal renal tubular architecture, 400 $\times$ ; scale bar = 50  $\mu$ m.

aspect of a much larger effect, preparing the body to defend against global ischemia and reperfusion injury.<sup>34</sup>

When sustained periods of aortic occlusion are necessary, P-REBOA can result in less rebound hypotension than C-REBOA. Balloon deflation precipitates rapid redistribution of circulating blood into distal vascular beds dilated from ischemia. This abrupt decrease in cardiac afterload combined with washout of ischemic metabolites further suppresses myocardial function and weakens vascular tone.<sup>35</sup> Taken together, these effects can cause abrupt hemodynamic collapse.<sup>36</sup> The need for repeat aortic occlusion to counter this collapse has been seen in both large animal models and clinically.<sup>12,35-37</sup> In the current study, the C-REBOA group demonstrated profound decreases in central MAP after balloon deflation, and even resulted in the death of one animal before the end of the study. In contrast, the P-REBOA group experienced smaller decreases in central aortic pressure after balloon deflation, with all animals maintaining an aortic MAP above the pre-hemorrhage baseline for the remainder of the study. Maintaining even a small amount of perfusion distal to the balloon can ameliorate tissue ischemia, rebound hypotension after balloon deflation and reperfusion injury, resulting in decreased morbidity and mortality.

### Limitations

Our model of P-REBOA using a conventional noncompliant balloon catheter to achieve partial aortic occlusion is not clinically applicable in its current form. This type of balloon architecture has a narrow diameter range that requires using fluoroscopy to size the balloon to the individual aorta. However, it was intentionally chosen to overcome an important limitation of more commonly used compliant spherical aortic occlusion balloons, where precise control of aortic pressure gradients is challenging if not impossible.<sup>18,24</sup> The elongated, cylindrical shape of the noncompliant balloon approximates the wall of the aorta across a longer length, which provides precise control over the degree of aortic occlusion. We were able to reproduce specified aortic pressure gradients with a high degree of fidelity in this study. Complete aortic occlusion generated a 90% proximal to distal aortic pressure gradient, rather than a 100% gradient, in the C-REBOA group. This observation might indicate a small amount of nonpulsatile distal aortic flow entering through collateral pathways or the inherent back pressure of the aorta below the point of occlusion. The 10%, rather than 0%, pressure gradient observed in the control group might represent a small amount of aortic occlusion created by the uninflated balloon catheter or the normal physiologic decrease in

MAP that is known to occur along the length of the aorta.<sup>38</sup>

The 50% gradient chosen for P-REBOA was selected as a starting point for our proof-of-concept study. However, it remains unclear how the pressure gradient achieved in this study relates to tissue perfusion at the organ level. Given the dynamic nature of blood pressure and flow, pressure gradient alone might not be a sufficient metric to ensure distal aortic blood flow within a desirable range in a true clinical scenario.<sup>18,24,39</sup> More work is needed to determine the optimal parameters to guide control of aortic blood flow to minimize hemorrhage and maintain distal tissue perfusion.

Our study duration was too short to examine the intermediate and long-term effects of C-REBOA vs P-REBOA in terms of ongoing resuscitation requirements and multi-organ dysfunction reported in other studies with short-term survival end points.<sup>11-13</sup> The short duration of the study also likely contributed to the limited histologic evidence of end-organ ischemia in all but the duodenum and kidneys, as well as the limited differences in inflammatory cytokine production we observed.

This study was conducted in a controlled hemorrhage model that does not assess the ability of P-REBOA to confer these benefits in the presence of uncontrolled, multifocal, or ongoing hemorrhage. In our previously published study of P-REBOA in uncontrolled hemorrhage, we saw that P-REBOA prevented the hemodynamic extremes associated with C-REBOA, but the presence of ongoing hemorrhage limited our ability to observe any benefits from preserved distal perfusion.<sup>22</sup> Partial REBOA might be suitable when control of major sources of hemorrhage has been achieved. Additionally, P-REBOA might be more practical when access to blood products and surgical capabilities is readily available. Additional development and refinement are needed before this technique is feasible outside of well-resourced hospitals.

Finally, the need for arterial access, radiographic imaging to confirm catheter position, and limited physician experience with endovascular techniques all stand as obstacles to the widespread use of REBOA.<sup>7,40-42</sup>

### CONCLUSIONS

In our proof-of-concept study in a swine model of hemorrhagic shock, P-REBOA maintained normal physiology better than C-REBOA, lessened the systemic impact of distal organ ischemia, and reduced hemodynamic instability, providing the potential for longer periods of intervention than are currently recommended with



C-REBOA. This study provides support for additional development of this technique in an effort to overcome the current limitations of C-REBOA. Overcoming the deleterious effects of prolonged aortic occlusion could further revolutionize the management of noncompressible torso hemorrhage, particularly closer to the point of injury and before hemodynamic collapse. Additional technological innovation is warranted to address the limitations of current catheter designs to facilitate implementation of P-REBOA in the clinical environment.

### Author Contributions

Study conception and design: Russo, Neff, Lamb, Cannon, Galante, Grayson, Williams

Acquisition of data: Russo, Neff, Lamb, Clement, Grayson, Williams

Analysis and interpretation of data: Russo, Lamb, Cannon, Galante, Clement, Grayson, Williams

Drafting of manuscript: Russo, Neff, Lamb, Neff, Galante, Clement, Grayson, Williams

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